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Viewpoint

Interferon gamma runs interference on persistent COVID-19

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SUMMARY

COVID-19 represents a collection of disease endotypes stemming from infection with SARS-CoV-2 and thus requires precision medicine approaches to target specific viral variants and stages of illness. In this issue, van Laarhoven et al.[1] describe five immunocompromised patients with prolonged COVID-19 successfully treated with interferon gamma (IFNγ).

The concept of endotype, first coined in 1966, has since been widely applied to diverse human diseases.[2] Fundamentally, the concept of endotype recognizes that diverse underlying mechanisms of pathogenesis produce the same clinically defined (easily observable) disease features. This framework partially explains why diseases lack uniform response to therapy. Like other infectious diseases, COVID-19 encompasses many endotypes which manifest as asymptomatic carriage, mild respiratory illness, acute respiratory distress syndrome (with low and high elasticity phenotypes), sepsis syndrome, and hyperinflammatory syndromes resembling macrophage activation syndrome/hemophagocytic lymphohistiocytosis (multisystem inflammatory syndrome in children [MIS-C] and adults [MIS-A]). The diverse endotypes are posited to be a function of variant and load of SARS-CoV-2 inoculum, host-intrinsic genetic/epigenetic characteristics, and unknown "environmental" determinants.[3] While complex, COVID-19 pathogenesis can be broadly conceptualized as failures in viral control (disease resistance) and failures in tolerating immunologic and non-immunologic aspects of host response to infection (disease tolerance)[4] (Figure 1A). These factors operate dynamically along different stages of disease and as a function of medical interventions.

Immunocompromised individuals are a heterogenous population of patients with severely impaired disease resistance who are uniquely vulnerable to poor COVID-19 outcomes.[5] The immune response necessary to achieve viral clearance of SARS-CoV-2 requires multiple intact and coordinated immune effector functions, among which there are multiple points of failure and opportunities for targeted intervention.[6] For example, as humoral immunity is essential for effective viral clearance and survival, passive immunization has repeatedly shown benefit in the subset of immunocompromised patients with defective humoral responses who may not have other comorbid immune failures. Herein, van Laarhoven and colleagues present a series of five immunocompromised patients with prolonged, severe COVID-19, unresponsive to commonly used enhancers of disease tolerance and resistance, who ultimately improved with IFNγ administration[1] (Figure 1B). This report is a prime example highlighting the growing awareness for the need of host- and mechanism-directed therapies (precision medicine) in managing COVID-19 and other sepsis syndromes.

The case series details five immunocompromised patients with prolonged, severe COVID-19. Two (patients 1 and 4) with underlying conditions impairing humoral immune responses (e.g., common variable immunodeficiency) were also noted clinically to have defective cellular immunity following SARS-CoV-2 infection as evidenced by HSV reactivation and invasive pulmonary aspergillosis. The other three patients were renal transplant recipients who received B cell-depleting agents that impair humoral immunity (e.g., rituximab or alemtuzumab) but were also on therapies—tacrolimus, mycophenolate mofetil, and corticosteroids—that generally impair immune function including T cell responses. Unsurprisingly, application of the current panoply of COVID-19 therapies, variably directed at disease resistance (passive immunization and remdesivir) and tolerance (dexamethasone and tocilizumab), did not impact clinical trajectory. Van Laarhoven and colleagues thus decided to augment cellular mechanisms of pathogen clearance by administering IFNγ. Following IFNγ, all five patients experienced reduction in detectable SARS-CoV-2 that corresponded to improved respiratory status. Four patients were discharged from intensive care, and three were extubated. Because immunopathology represents one endophenotype of COVID-19 thought to be IFNγ-driven, van Laarhoven et al. were vigilant that IFNγ may provoke a hyperinflammatory response but found no

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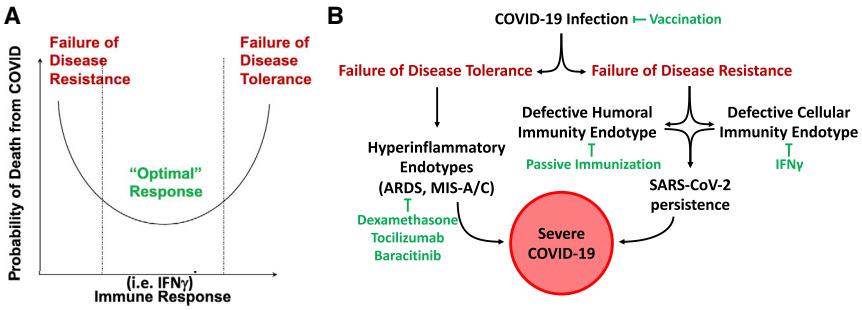

Figure 1. COVID-19 disease is composed of several incompletely defined endotypes

Endotypes can be broadly characterized as failures in disease resistance, such as inborn or acquired defects in pathogen clearance, and/or failures in disease tolerance, such as exuberant inflammatory responses or impaired tolerance to inflammatory damage, which both lead to increased probability of death from SARS-CoV-2 infection.

(A) Failure to produce sufficient IFNγ, for example, leads to defects in pathogen clearance, while failure to restrain IFNγ production leads to immunopathology.

(B) Immunosuppressive medications target hyperinflammatory disease endotypes while passive immunization promotes viral clearance in patients with defective humoral immunity. Van Laarhoven et al.[1] utilized IFNγ to target likely defects in cellular immunity when treatments targeting humoral immunity and hyperinflammation failed.

uniform evidence of worsened systemic inflammation.[1]

IFNγ is approved for treatment of chronic granulomatous disease and malignant osteopetrosis and has been used in patients with HIV, mycobacterial infections, invasive fungal infections, and malignancies[7]. A role for exogenous IFNγ in COVID-19 is biologically plausible, as patients with COVID-19 have T cell lymphopenia, CD4 responses skewed away from T_H1, CD8 senescence, and impaired IFNγ production[8]. Several other groups have used IFNγ in patients with COVID-19. As in this series, Lukaszewicz et al. found IFNγ improved SARS-CoV-2 clearance and clinical status in a patient with rheumatoid arthritis and Sjögren syndrome on rituximab who had worsened despite convalescent plasma[9]. A patient with endogenous anti-IFNγ antibodies was treated for COVID-19 with plasma exchange and exogenous IFNγ, but interestingly he did not have severe COVID-19 symptoms.[10] HLA-DR expression may be useful as a biomarker to define an endotype that benefits from IFNγ, as IFNγ restored monocyte activation and improved ventilator-associated pneumonia in otherwise immunocompetent COVID-19 patients with decreased monocyte HLA-DR[11]. However, as one would predict from the U-shaped biology of IFNγ (Figure 1A), studies are conflicting in terms of whether greater IFNγ production is associated with worsened outcomes in severe COVID-19. Indeed, the anti-IFNγ monoclonal antibody emapalumab is being investigated in clinical trials (NCT04324021).

This present case series is limited by small numbers and observational design without controls. Another limitation of this study is that a mechanistic link from IFNγ to augmented cellular immunity and viral clearance is not definitively established. Prior to IFNγ administration, viral cultures were negative in patients 1 and 3, inconsistently positive in patient 2, and not performed for patients 4 and 5. As PCR detection of viral RNA may not represent infectious virus, it is uncertain whether IFNγ is beneficial due to augmented disease resistance via viral clearance or by another mechanism. Rather, IFNγ may improve clearance of inflammatory but non-infectious viral pathogen-associated molecular patterns or contribute to other mechanisms of disease tolerance. Nonetheless, the clinical decision-making process and arrival at therapeutic IFNγ highlights the need for a precision approach to COVID-19 specifically, and to sepsis syndromes in general.

As disease endotypes are better defined, aided by technologic advances and spurred by wider recognition that clinically defined diseases are comprised of an array of complex pathophysiologic phenotypes that require multidisciplinary approaches, we have observed advances in the medical management of psychiatric illness, autoimmunity, asthma, cancer, and other conditions. The COVID-19 pandemic presents scientists with an unprecedented opportunity to define and understand endotypes of infectious disease. "Targeted" therapies will likely be reliable only in certain subsets of patients (their respective "targets") and identifying clinical factors and biomarkers that define endotypes of COVID-19 will aid clinical trial design and improve likelihood of successful outcomes. For COVID-19, the question remains who should we treat, what with, and when?

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DECLARATIONS OF INTEREST

The authors have no conflicts of interest to declare.

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